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Oral and Dental Late Effects after Pediatric Stem Cell Transplantation

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Many of the oral and dental sequelae to chemotherapy and radiation are irreversible, and for pediatric cancer patients oral sequelae and discomfort related to their treatment can have long-term consequences. Conditioning for stem cell transplantation (SCT) has been shown to cause more severe disturbances compared to most chemotherapy protocols [1]. On the other hand, efforts that have been made to reduce the intensity of conditioning, for example, use of busulfan for total-body irradiation (TBI) will reduce the prevalence of salivary dysfunction, and dose fractionation of TBI will result in less salivary dysfunction as well as less dental developmental disturbances. Knowledge of the oral and dental late effects is important because many children are affected and there often is a need for early intervention. This review will focus on the increased risk of developing dental caries, salivary dysfunction, and developmental changes, including damage to developing teeth.

An evaluation of oral health is a part of the preparation for stem cell transplantation in many centers. This is warranted, because many children have preexisting oral diseases. In a group of 259 children preparing for SCT, oral diseases were diagnosed in 58% [2].

DENTAL CARIES

Studies with longer follow-up time have shown an increased risk for dental caries among long-term survivors after childhood cancer. One study particularly pointed out the period of induction therapy as a period of increased caries risk. Three particular risk factors can be identified: radiation therapy, including salivary glands, for example TBI [3], if the child has high caries prevalence at the start of cancer therapy [4], and lack of caries preventive care during the first year of cancer treatment [5].

We have preliminary data from a nationwide population-based study linking records from the Danish Cancer Registry with records from the national database on oral health. The study included 7-, 12- and 15-year-old children. Those whose dental examination had been preceded by a cancer diagnosis were compared with children without a cancer diagnosis. Children diagnosed with cancer before the age of 5 years did not have increased caries prevalence in permanent teeth at age 12. Children diagnosed with cancer between 5 and 6 years of age had an increased prevalence of caries in smooth tooth surface at age 12 years (prevalance rate [PR] = 1.59; 95% confidence interval [CI]: 1.09-2.31). For children diagnosed with cancer at 5 or 6 years of age and who received radiation therapy the PR of caries in 1 or more smooth tooth surface was significantly increased. We investigated 2 cohorts of children with cancer: those born between 1993 and 1997 had a lower prevalence of dental caries than those children with cancer born 1984-1988. This may be the result from development of targeted dental treatment procedures and oral hygiene guidelines for children undergoing cancer therapy during the early 1990s. Our results indicate an increased caries risk in children 5 or 6 years at diagnosis, those treated with radiation therapy, and a decreasing trend of dental caries in children with cancer [6].

There are effective programs for caries prevention based on the use of fluorides, antibacterial substances such as chlorhexidine, and effective plaque control [7]. Recent developments that will be commercially available are fluoride slow release devices that do not require patient involvement except for periodic replacement, thus reducing the effect of patient compliance [8].

SALIVARY DYSFUNCTION

Children conditioned with TBI are at risk to develop salivary dysfunction [9]. Children conditioned with single-dose TBI will have a permanently damaged salivary secretion rate. Many of the long-term survivors will have stimulated salivary secretion rated below

0.5 mL/min, which is a cutoff point for increased risk for dental caries. We also have preliminary data from a comparison of long-term survivors conditioned with 10 Gy single-dose TBI to those conditioned with 3 × 4 Gy fractionated TBI (fTBI). The results show that at the 1-year follow-up children treated with fTBI had a stimulated salivary secretion rate. Children treated with fTBI had a secretion rate of 1.0 ± 0.5 mL/min, a 10% reduction compared to baseline; the TBI-group had 0.5 ± 0.3 mL/min, a 54% reduction ($P < .001$). The unstimulated salivary secretion rate in the fTBI group was 0.4 ± 0.3 mL/min, a 13% reduction compared to baseline, and in the TBI group, 0.1 ± 0.1 mL/min, a 66% reduction ($P = .0011$). The incidence of chronic graft-versus-host was similar in the 2 groups, and did not affect the salivary secretion rate. One particular aspect of salivary dysfunction in children is that they rarely complain about mouth dryness, even though they objectively have a very low salivary output. An interview that focuses on everyday situations may reveal signs and symptoms of mouth dryness. We investigated 53 children surviving more than 2 years. Salivary gland dysfunction was present in 35% of the patients. Seventy-nine percent of the patients expressed 1 or more symptom of dry mouth, and 49% gave at least 2 answers indicating dry mouth. The number of complaints increased with age at examination ($P < .05$). A reduction in stimulated salivary secretion rate compared with the year before was correlated to 2 or more complaints of xerostomia ($P < .01$). The presence of dry mouth at night or on awakening was indicative of both low salivary function ($P < .001$). In contrast to the situation in adults, there is a correlation between the expression of subjective complaints of xerostomia and salivary gland dysfunction in children [10].

DISTURBANCES IN DENTAL DEVELOPMENT

Disturbances in dental development and particularly in root development after cancer therapy is characterized by arrested root development with short V-shaped roots, arrested root development with premature apical closure, microdontia, and also an increased incidence of aplasia. Children subjected to radiation therapy at an early age are particularly at risk. In a comparison between children treated with chemotherapy protocols for malignant diseases and children conditioned with 10 Gy of TBI before SCT, Näsman et al [11] found a mean number of 4.1 ± 5.0 teeth were affected by disturbances in enamel mineralization. In the TBI group, 4.6 ± 4.6 teeth were affected, both significantly higher compared with the healthy control group 0.7 ± 1.4 ($P < .05$). White/cream-colored opacities were most commonly diagnosed in all 3 groups, followed by yellow/brown opacities. Twelve percent of the children treated with TBI and 8% treated with chemotherapy exhibited hypoplasia. In a study of children with poor-risk neuroblastoma treated with high-dose chemotherapy and autologous SCT with or without TBI before 5.8 years of age, all children had disturbances in dental development. Children in the TBI group had 2 to 12 missing permanent teeth (mean = 6.6), and 27% of all permanent teeth were missing. In those not treated with TBI, 4.8% of the teeth were missing.

A combination of busulfan (BU) with a lower dose of cyclophosphamide (CY) has been used in different types of leukemia and other diseases with acceptable levels of toxicity. We have preliminary data from a comparison of the effect of BU (16 mg/kg) and CY (120 mg/kg) and TBI 10 Gy single dose and CY (120 mg/kg) on dental development. Eighty-one recipients of allogeneic SCT were studied. The mean age in the TBI/CY group was 8.5 ± 4.2, and in the BU/CY group, 6.1 ± 4.0. Adjusted for the age difference children conditioned with BU/CY had significantly more aplasia (including third molar) and teeth reduced in size compared those conditioned with single-dose TBI (Figure 1). Preliminary data reveal, on the other hand, that the children conditioned with BU/CY had a significantly better salivary secretion rate 1 year after SCT compared to those conditioned with TBI/CY (Figure 1).

Children who are long-term survivors after SCT may require orthodontic treatment because of different types of malocclusions [12]. The treatment may be complicated because of disturbances in dental development, particularly in the root development. We have studied the course of treatment in 10 children and not found an increased risk of complications because of the orthodontic treatment. Treatment start should be postponed until 2 years after completion of cancer therapy [13].

In conclusion, this review shows that with reduced intensity conditioning the prevalence of oral and dental late effects will be less severe in the future.

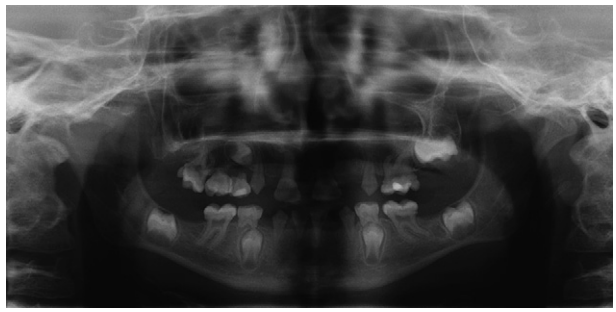

Figure 1. Panoramic radiograph at 9 years showing the dentition of a 9-year old boy with MDS conditioned with BU/CY for SCT at 7 months of age. Severe disturbances of development of dentition and alveolar processes can be seen. Eighteen of 32 permanent teeth are missing. Enamel hypoplasia as well as disturbances in root development can be seen on all first permanent molars. The roots of the primary teeth are all resorbed.

Conditioning with BU and fTBI has less toxic effects of salivary glands. Many children preparing for SCT have preexisting oral diseases and those with high caries prevalence at risk to develop new lesions. In children subjected to TBI there is a strong correlation between xerostomia (the subjective feeling) and a reduced salivary secretion rate. Children should be asked specific questions regarding the subjective feeling of xerostomia.

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